Commentary

Anti-atherogenic effects of fibrates in type 2 diabetes

Philip Barter

Royal Adelaide Hospital, Adelaide, South Australia, Australia

Correspondence: Philip Barter, philip.barter@adelaide.edu.au

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Abstract

Type 2 diabetes is an increasing cause of premature coronary heart disease. Several trials with lipid-modifying therapy have included sufficient numbers of diabetics to indicate that treatment of diabetic dyslipidaemia with either fibrates or statins reduces the risk of future coronary events in such patients. However, until recently no reported study had been designed specifically to investigate the effects of intervening in patients with type 2 diabetes. The Diabetes Atherosclerosis Intervention Study (DAIS) is an angiographic study in which 418 diabetic subjects were randomized to micronised fenofibrate or placebo groups. After 3 years of treatment, the fenofibrate group had a significantly reduced rate of progression of coronary atherosclerosis. This study, when considered with the results of other studies that have included diabetics, has important implications for the treatment of diabetic dyslipidaemia. The evidence that is currently available supports a place for both fibrates and statins, either as monotherapy or in combination, in the treatment of diabetic dyslipidaemia.

Keywords atherosclerosis, diabetes, fenofibrate, fibrate, statin

There is a worldwide epidemic of type 2 diabetes that is contributing to a disturbing increase in the incidence of coronary heart disease (CHD) in many countries. The precise mechanisms by which type 2 diabetes causes CHD is uncertain, although the dyslipidaemia that is common in this form of diabetes almost certainly has a role. Indeed, several large-scale intervention studies with lipid-modifying therapy have included a sufficient number of type 2 diabetics to be able to conclude that, as in non-diabetics, treatment of the abnormal lipids in type 2 diabetes reduces future coronary risk. These studies have used both statins [1–3] and fibrates [4,5] as the therapeutic intervention.

Intervention studies that have included type 2 diabetics

Statin trials

The Scandinavian Simvastatin Survival Study (4S) [1] was a secondary prevention study that included 201 patients with type 2 diabetes. The diabetics in the active treatment group had a 55% decrease in future coronary events ($P = 0.002$). The Cholesterol and Recurrent Events (CARE) trial included 603 diabetic subjects [2]. Coronary event reduction in the diabetics on pravastatin was 25% ($P = 0.05$). In the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study [3], another secondary prevention trial, there were 782 type 2 diabetics. In this study, active treatment with pravastatin reduced coronary events in the diabetics by 19% (not significant).

Fibrate trials

The Helsinki Heart Study [4] was a primary prevention trial using gemfibrozil as the active agent. There were 135 subjects with type 2 diabetes in whom active treatment reduced adverse coronary events by 68%, although because of the small sample size, this result was not statistically significant. The Veterans Administration High Density Lipoprotein Intervention Trial (VA-HIT) [5] also used gemfibrozil as the active agent in subjects with existing CHD.

4S = Scandinavian Simvastatin Survival Study; DAIS = Diabetes Atherosclerosis Intervention Study; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; VA-HIT = Veterans Administration High Density Lipoprotein Intervention Trial.
CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

In this study there were 627 type 2 diabetics in whom gemfibrozil reduced future coronary events by 24% ($P = 0.05$).

Until recently, no reported study had been conducted exclusively in patients with type 2 diabetes. It is therefore of great interest to see the results of the Diabetes Atherosclerosis Intervention Study (DAIS), which have recently been published [6].

Diabetes Atherosclerosis Intervention Study

DAIS included 418 men and women with type 2 diabetes who were randomised to receive micronised fenofibrate (200 mg/day), or placebo, and followed for 3 years. Half of the participants had previous clinical coronary heart disease but all had at least one lesion visible on coronary angiography. In this angiographic study, the primary endpoints were changes in minimum lumen diameter, mean segment diameter, and mean percentage stenosis.

The baseline lipid profiles of the active treatment and placebo groups were well matched and were typical of reported profiles in type 2 diabetes. Glycaemic control was acceptable by recognized standrads throughout the study in both groups. Fenofibrate had predictable effects on the plasma lipids, with moderate but significant decreases in total and low-density lipoprotein (LDL) cholesterol, a more substantial and significant decrease in plasma triacylglycerol, and a significant increase in high-density lipoprotein (HDL) cholesterol. In terms of the primary endpoints, the fenofibrate group had a 40% reduction in progression of angiographic changes as judged by minimum lumen diameter ($P = 0.029$), 42% less progression as judged by changes in percentage diameter stenosis ($P = 0.02$), and 25% less progression in mean segment diameter ($P = 0.171$, not significant).

Because of the relatively small numbers of participants in a trial lasting 3 years, clinical events were not primary endpoints. It was therefore predictable that differences in clinical endpoints between the fenofibrate and placebo groups were not statistically significant. However, it was encouraging to note that when considering a composite clinical endpoint (death, myocardial infarction, coronary angioplasty, coronary bypass surgery, and hospitalisation for angina) there were 38 events in the fenofibrate group compared with 50 in the placebo group. Although not statistically significant, the magnitude of the decrease in clinical events was similar to that observed in the diabetics in other trials.

Comparison of DAIS with other angiographic studies

Overall, the reduction in progression of angiographic changes observed in the fenofibrate group in DAIS is of the same order as reported for non-diabetics treated with other agents in several trials [7–9]. Previous studies of this type in diabetics have not been reported.

Implications of DAIS

The typical dyslipidaemia in type 2 diabetes is a moderate increase in plasma triacylglycerol, a decrease in HDL cholesterol and a total LDL cholesterol that is normal or mildly elevated. Fenofibrate has been reported to decrease plasma triacylglycerol and increase HDL cholesterol and, in contrast with some other fibrates, also promotes a modest decrease in LDL cholesterol. It can therefore be argued that such an agent might be an appropriate therapy for type 2 diabetics. The results of DAIS add support to this view by clearly demonstrating a slowing of coronary atherosclerosis during 3 years of treatment with fenofibrate. The results are also most encouraging with regard to the possible outcomes in continuing, long-term, hard-endpoint trials using fenofibrate in type 2 diabetics.

One of these is the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, in which more than 9000 type 2 diabetics have been randomised, double blind to placebo or micronised fenofibrate. This 5-year study in which the primary endpoint is coronary mortality is due to be completed in 2004/2005. The FIELD study will provide a clear answer to the role of fenofibrate in the prevention of CHD in diabetes. The results of DAIS greatly strengthen the justification for conducting the FIELD Study.

Statins and fibrates in the treatment of diabetic dyslipiaemia

Considering the evidence from large-scale hard endpoint trials that have included diabetics, and the recent evidence from DAIS, it is apparent that treatment with both fibrates and statins has the capacity to slow the progression of coronary atherosclerosis and to reduce the future incidence of coronary events. A question that frequently arises is: Should we use a statin or a fibrate as the agent of first choice to treat the dyslipidaemia in type 2 diabetes? On the basis of current evidence, it is difficult to give a categorical answer. However, it is possible to interpret the existing evidence as supporting a case for using each class of drug.

There are two circumstances in which the choice of drug is reasonably clear. In a diabetic with elevated LDL cholesterol, the evidence from 4S [1] supports the use of a statin as the drug of first choice. In contrast, if the LDL level is low in a lipid profile characterized by a low HDL cholesterol and elevated triacylglycerol, the evidence from VA-HIT [5] supports the use of a fibrate as the agent of first choice. However, there is a substantial group of type 2 diabetics in whom the levels of both plasma triacylglycerol and LDL cholesterol are higher than desirable and with low HDL cholesterol. Treatment with a statin will undoubtedly correct the LDL cholesterol but might leave the HDL low. Treatment with a fibrate might correct the HDL cholesterol/triacylglycerol abnormality but might be unable to lower LDL cholesterol to recommended target levels for diabetics. In such cases, many physicians will opt to use combination therapy with a statin and a fibrate. However, it

should also be noted that there is still no long-term evidence on the safety or effectiveness of this combination. Therefore, as potentially serious adverse effects might occasionally occur when combining a fibrate and statin, this combination should be offered only to patients who are at high coronary risk.

Competing interests

None declared.

References

1. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G: **Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease.** *Diabetes Care* 1997, **20**:614-621.
2. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E: **Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol And Recurrent Events (CARE) trial.** *Circulation* 1998, **98**:2513-2519.
3. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group: **Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels.** *New Engl J Med* 1998, **339**:1349-1357.
4. Koskinen P, Manttari M, Maninen V, Huttunen JK, Heinonen OP, Frick MH: **Coronary heart disease in NIDDM patients in the Helsinki Heart Study.** *Diabetes Care* 1992, **15**:820-825.
5. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group: **Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol.** *New Engl J Med* 1999, **341**:410-418.
6. Diabetes Atherosclerosis Intervention Study Investigators: **Effect of fenofibrate on progression of coronary in artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study.** *Lancet* 2001, **357**:905-910.
7. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT: **Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apoB.** *New Engl J Med* 1990, **323**:1289-1298.
8. Ericsson CG, Hamsten A, Nilsson J, Grip L, Svane B, de Faire U: **Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male post-infarction patients.** *Lancet* 1996, **347**:849-853.
9. Waters D: **Lessons from coronary atherosclerosis 'regression' trials.** *Cardiol Clin* 1996, **14**:31-50.